CHAPTER 2

DIURETICS AND ANTI DIURETICS

YEAR III PHARM.D
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Anatomy and Physiology of Renal system

- The nephron is the most important part of the kidney that regulates fluid and electrolytes.

- Urine formation:
  1. Glomerular filtration rate = 180L/day
  2. Tubular re-absorption (around 98%)
  3. Tubular secretion
► How could urine output be increased?

↑ Glomerular filtration Vs ↓ Tubular reabsorption (the most important clinically)

If you increase the glomerular filtration → increase tubular reabsorption (so you can’t use glomerular filtration)

► Purpose of Using Diuretics

1. To maintain urine volume (e.g.: renal failure)

2. To mobilize edema fluid (e.g.: heart failure, liver failure, nephrotic syndrome)

3. To control high blood pressure.
Percentage of reabsorption in each segment:
- Proximal convoluted tubule 60-70%
- Thick portion of ascending limb of the loop of Henle 25%
- Distal convoluted tubule 5-10%
- Cortical collecting tubule 5% (Aldosterone and ADH)
Physiology of tubular reabsorption

The filtrate here is isotonic

The filtrate here is hypertonic
The organic acid and base secretory systems secrete a variety of organic acids (including most diuretic drugs) from the bloodstream into the lumen of the proximal tubule.
The best way to classify diuretics is to look for their Site of action in the nephron.

A) Diuretics that inhibit transport in the Proximal Convoluted Tubule (Osmotic diuretics, Carbonic Anhydrase Inhibitors)

B) Diuretics that inhibit transport in the Medullary Ascending Limb of the Loop of Henle (Loop diuretics)

C) Diuretics that inhibit transport in the Distal Convoluted Tubule (Thiazides: Indapamide, Metolazone)

D) Diuretics that inhibit transport in the Cortical Collecting Tubule (Potassium sparing diuretics)
Figure 15-2. Tubule transport systems and sites of action of diuretics. Circles with arrows denote known ion cotransporters that are targets of the diuretics indicated by the numerals. Question marks denote preliminary or incompletely documented suggestions for the location of certain drug effects. (Reproduced, with permission, from Katzung BG [editor]: Basic & Clinical Pharmacology. 8th ed. McGraw-Hill, 2001.)
Figure 22.2
Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.
A. Diuretics that inhibit transport in the Convoluted Proximal Tubule

1. Osmotic Diuretics (e.g.: Mannitol)

**Mechanism of action:** They are hydrophilic compounds that are easily filtered through the glomerulus with little re-absorption and thus increase urinary output via osmosis.

**PK:** Given parenterally. If given orally it will cause osmotic diarrhea.

**Indications:**
- to decrease intracranial pressure in neurological condition
- to decrease intraocular pressure in acute glaucoma
- to maintain high urine flow in acute renal failure during shock

**Adverse Reactions:**
- Extracellular water expansion may complicate heart failure and produce pulmonary edema.
- Dehydration
- Hypernatremia due to loss more water than sodium

**Contraindication:**
1- heart failure
2- renal failure
2. **Carbonic Anhydrase Inhibitors** (Acetazolamide (Oral); Dorzolamide (Ocular); Brinzolamide (Ocular))

**Mechanism of action** Simply inhibit reabsorption of sodium and bicarbonate.

- **Inhibition of HCO\textsubscript{3} reabsorption** → metabolic acidosis.
- **HCO\textsubscript{3} depletion** → enhance reabsorption of Na and Cl → hyperchloremia.
- **Reabsorption of Na** → ↑ negative charge inside the lumen → ↑K secretion
Clinical uses

• Weak diuretic: because depletion of $\text{HCO}_3$ → enhance reabsorption of Na and Cl

• In glaucoma:
  ✓ The ciliary process absorbs $\text{HCO}_3$ from the blood.
  ✓ $\uparrow \text{HCO}_3$ → $\uparrow$ aqueous humor.
  ✓ Carbonic anhydrase inhibitors prevent absorption of $\text{HCO}_3$ from the blood.

• Urinary alkalinization: to increase renal excretion of weak acids e.g. cystin and uric acid.

• In metabolic alkalosis.

• Epilepsy: because acidosis results in $\downarrow$ seizures.

• Acute mountain sickness.

• Benign intracranial hyper tension.

Dorzolamide and brinzolamide are mixed with $\beta$ blockers (Timolol) to treat glaucoma (as topical drops)
Side Effects of Acetazolamide:

Sedation and drowsiness; Hypersensitivity reaction (because it contains sulfur)
Acidosis (because of decreased absorption of $\text{HCO}_3^-$); Renal stone (because of alkaline urine);
Hyperchloremia, hyponatremia and hypokalemia
B. Diuretics Acting on the Thick Ascending Loop of Henle (loop diuretics) High ceiling (most efficacious)

- e.g. Furosemide (Lasix\textsuperscript{R}), Torsemide, Bumetanide (Bumex\textsuperscript{R}), Ethacrynic acid.

**Pharmacodynamics:**
1) **Mechanism of Action**: Simply inhibit the coupled Na/K/2Cl cotransporter in the loop of Henle. Also, they have potent pulmonary vasodilating effects (via prostaglandins).
2) They eliminate more water than Na.
3) They induce the synthesis of prostaglandins in kidney and NSAIDs interfere with this action.

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They are the best diuretics for 2 reasons:
1- they act on thick ascending limb which has large capacity of reabsorption.
2- action of these drugs is not limited by acidosis
Figure 15-2. Tubule transport systems and sites of action of diuretics. Circles with arrows denote known ion cotransporters that are targets of the diuretics indicated by the numerals. Question marks denote preliminary or incompletely documented suggestions for the location of certain drug effects. (Reproduced, with permission, from Katzung BG [editor]: Basic & Clinical Pharmacology. 8th ed. McGraw-Hill, 2001.)
In loop diuretics and thiazides:
The body senses the loss of Na in the tubule.

This lead to compensatory mechanism (the body will try to reabsorb Na as much as possible).

So the body will increase synthesis of aldosterone leading to:
1- increase Na absorption
2- hypokalemia
3- alkalosis
2. Side effects:
   **Ototoxicity**; Hypokalemic metabolic alkalosis; hypocalcemia and hypomagnesemia; hypochloremia; Hypovolemia; hyperuricemia (the drugs are secreted in proximal convoluted tubule so they compete with uric acid’s secretion) hypersensitivity reactions(contain sulfur)

3. Therapeutic Uses
   a) Edema (in heart failure, liver cirrhosis, nephrotic syndrome)
   b) Acute renal failure
   c) Hyperkalemia
   d) Hypercalcemia
Dosage of loop diuretics:

- **Furosemide**
  - Taken orally or i.v
  - If taken orally only 50% is absorbed

- **Torsemide**
  - Taken orally
  - Better absorption
  - Fast onset of action
  - $t_{1/2}$ increased

- **Bumetanide (Bumex®)**
  - Taken orally
  - 40 times potent than furosemide
  - Fast onset
  - Short duration of action

- **Dosage**
  - Furosemide: 20-80 mg
  - Torsemide: 2.5-20 mg
  - Bumetanide: 0.5-2.0 mg
Figure 22.6
Relative changes in the composition of urine induced by loop diuretics.
Figure 22.4
Relative changes in the composition of urine induced by thiazide diuretics.
C. Diuretics that Inhibit Transport in the Distal Convoluted Tubule (e.g.: Thiazides and Thiazide-like (Indapamide; Metolazone))

**Pharmacodynamics:**
- Mechanism of action: Inhibit Na\(^+\) via inhibition of Na\(^+\)/Cl\(^-\) cotransporter.
- They have natriuretic action.

**Side effects:**
- No ototoxicity; hypercalcemia due to ↑PTH, more hyponatremia; hyperglycemia (due to both impaired pancreatic release of insulin and diminished utilization of glucose) hyperlipidemia and hyperurecemia; hypokalemic metabolic alkalosis
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Clinical uses:

a) Hypertension Drug of Choice (Hydrochlorothiazide; Indapamide (Natrilex®))
b) Refractory Edema (doesn’t respond well to ordinary treatment) together with the Loop diuretics (Metolazone).
c) Nephrolithiasis (Renal stone) due to idiopathic hypercalciuria.
d) hypocalemia.
e) Nephrogenic Diabetes Insipidus. (it decreases flow of urine \(\rightarrow\) more reabsorption)

Indapamide is a potent vasodilator
<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Urine</th>
<th>Body pH</th>
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<tbody>
<tr>
<td></td>
<td>NaCl</td>
<td>NaHCO₃</td>
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<tr>
<td>Carbonic anhydrase inhibitors</td>
<td>↑</td>
<td>↑↑↑</td>
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<tr>
<td>Loop diuretics</td>
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<td>Thiazides</td>
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<tr>
<td>Potassium-sparing diuretics</td>
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D. Diuretics that inhibit transport in the Cortical Collecting Tubule (e.g. potassium sparing diuretics).

Classification of Potassium Sparing Diuretics:

A) Direct antagonist of mineralocorticoid receptors (Aldosterone Antagonists e.g. spironolactone (Aldactone\textsuperscript{R}) or

B) Indirect via inhibition of Na\textsuperscript{+} influx in the luminal membrane (e.g. Amiloride, Triamterene)

**They are very important to balance K\textsuperscript{+} in the body**
Spironolactone (Aldactone®)

- Synthetic steroid acts as a competitive antagonist of aldosterone with a slow onset of action.

- **Mechanism of action:** Aldosterone cause ↑K and H⁺ secretion and ↑Na reabsorption.

- The action of spironolactone is the opposite
Clinical Uses of K+ sparing Diuretics:

- In states of primary aldosteronism (e.g. Conn’s syndrome, ectopic ACTH production) or secondary aldosteronism (e.g. heart failure, hepatic cirrhosis, nephrotic syndrome)
- To overcome the hypokalemic action of diuretics
- Hirsutism (the condensation and elongation of female facial hair) because it is an antiandrogenic drug.
**Side effects:**

- Hyperkalemia (sometimes it’s useful otherwise it’s a side effect).
- Hyperchloremic *(it has nothing to do with Cl)* metabolic acidosis
- Antiandrogic effects (e.g. gynecomastia: breast enlargement in males, impotence) by spironolactone.
- Triametrene causes kidney stones.

**Diuretics Combination preparations**

theses are anti-hypertensive drugs:

- Dyazide\(^R\) = Triametrene 50 mg + Hydrochlorothiazide HCT 25 mg
- Aldactazide\(^R\) = Spironolactone 25 mg + HCT 25 mg
- Moduretic\(^R\) = Amiloride 5 mg + HCT 50 mg

- Note: HCT to decrease hypertension and K sparing diuretics to overcome the hypokalemic effect of HCT
- Contraindications: Oral K administration and using of ACE inhibitors
Synthesis of ADH

- It is synthesized as pre-prohormone and processed into a nonapeptide (nine amino acids).
  - Six of the amino acids form a ring structure, joined by disulfide bonds.
  - It is very similar in structure to oxytocin, differing only in amino acid #3 and #8.
- ADH synthesized in the cell bodies of hypothalamic neurons in the supraoptic nucleus
- ADH is stored in the neurohypophysis (posterior pituitary)—forms the most readily released ADH pool
Hypothalamus and posterior pituitary
Structure of ADH

Antidiuretic hormone (ADH)

cys-tyr-phe-gln-asn-cys-pro-arg-gly-NH$_2$
Synthesis of ADH

- Mechanical disruption or the neurohypohyseal tract by trauma, tumor, or surgery temporarily causes ADH deficiency.
- ADH will be restored after regeneration of the axons (about 2 weeks).
- But if disruption happens at a high enough level, the cell bodies die in the hypothalamus resulting in permanent ADH deficiency.
Antidiuretic Hormone: ADH

- ADH is also known as arginine vasopressin (AVP = ADH) because of its vasopressive activity, but its major effect is on the kidney in preventing water loss.
ADH: conserve body water and regulate tonicity of body fluids

- Regulated by osmotic and volume stimuli
- Water deprivation increases osmolality of plasma which activates hypothalamic osmoreceptors to stimulate ADH release
Primary action of ADH: antidiuresis

- ADH binds to V2 receptors on the peritubular (serosal) surface of cells of the distal convoluted tubules and medullary collecting ducts.
- Via adenylate cyclase/cAMP induces production and insertion of AQUAPORIN into the luminal membrane and enhances permeability of cell to water.
- Increased membrane permeability to water permits back diffusion of solute-free water, resulting in increased urine osmolality (concentrates urine).
ADH: conserve body water and regulate tonicity of body fluids

- Regulated by osmotic and volume stimuli
- Water deprivation increases osmolality of plasma which activates hypothalmic osmoreceptors to stimulate ADH release
Secretion of ADH

- The biological action of ADH is to conserve body water and regulate tonicity of body fluids.
- It is primarily regulated by osmotic and volume stimuli.
- Water deprivation increases osmolality of plasma which activates hypothalmic osmoreceptors to stimulate ADH release.
Secretion of ADH

- Conversely, water ingestion suppresses osmoreceptor firing and consequently shuts off ADH release.
- ADH is initially suppressed by reflex neural stimulation shortly after water is swallowed.
- Plasma ADH then declines further after water is absorbed and osmolality falls.
Pathway by which ADH secretion is lowered and water excretion raised when excess water is ingested
Secretion of ADH—osmolality control

- If plasma osmolality is directly increased by administration of solutes, only those solutes that do not freely or rapidly penetrate cell membranes, such as sodium, cause ADH release.
- Conversely, substances that enter cells rapidly, such as urea, do not change osmotic equilibrium and thus do not stimulate ADH release.
- ADH secretion is exquisitely sensitive to changes in osmolality.
- Changes of 1-2% result in increased ADH secretion.
Secretion of ADH—hemodynamic control

- ADH is stimulated by a decrease in blood volume, cardiac output, or blood pressure.
- Hemorrhage is a potent stimulus of ADH release.
- Activities, which reduce blood pressure, increase ADH secretion.
- Conversely, activities or agents that increase blood pressure, suppresses ADH secretion.
Secretion of ADH

- Hypovolemia is perceived by “pressure receptors” -- carotid and aortic baroreceptors, and stretch receptors in left atrium and pulmonary veins.
- Normally, pressure receptors tonically inhibit ADH release.
- Decrease in blood pressure induces ADH secretion by reducing input from pressure receptors.
- The reduced neural input to baroreceptors relieves the source of tonic inhibition on hypothalamic cells that secrete ADH.
- Sensitivity to baroreceptors is less than osmoreceptors—senses 5 to 10% change in volume
Hypothalamus, posterior pituitary and ADH secretion—connection with baroreceptors
Secretion of ADH

- Hypovolemia also stimulates the generation of renin and angiotensin directly within the brain.
- This local angiotensin II enhances ADH release in addition to stimulating thirst.
- Volume regulation is also reinforced by atrial natriuretic peptide (ANP).
- When circulating volume is increased, ANP is released by cardiac myocytes, this ANP along with the ANP produced locally in the brain, acts to inhibit ADH release.
Secretion of ADH

- The two major stimuli of ADH secretion interact.
- Changes in volume reinforce osmolar changes.
- Hypovolemia sensitizes the ADH response to hyperosmolarity.
Actions of ADH

- The major action of ADH is on renal cells that are responsible for reabsorbing free (osmotically unencumbered) water from the glomerular filtrate.
- ADH responsive cells line the distal convoluted tubules and collecting ducts of the renal medulla.
- ADH increases the permeability of these cells to water.
- The increase in membrane permeability to water permits back diffusion of water along an osmotic gradient.
- ADH significantly reduces free-water clearance by the kidney.
Actions of ADH

- ADH action in the kidney is mediated by its binding to V2 receptors, coupled to adenylate cyclase and cAMP production.
- cAMP activates protein kinase A which prompts the insertion of water channels into the apical membrane of the cell.
- When ADH is removed, the water channels withdraw from the membrane and the apical surface of the cell becomes impermeable to water once again.
Actions of ADH

- This mechanism of shuttling water channels into and out of the apical membrane provides a very rapid means to control water permeability.
- The basolateral membrane of the ductal cells are freely permeable to water, so any water that enters via the apical membrane exits the cell across the basolateral membrane, resulting in the net absorption of water from the tubule lumen into the peritubular blood.
Actions of ADH

- Water deprivation stimulates ADH secretion, decreases free-water clearance, and enhances water conservation.
- ADH and water form a negative feedback loop.